A novel role for epidermal growth factor receptor tyrosine kinase and its downstream endoplasmic reticulum stress in cardiac damage and microvascular dysfunction in type 1 diabetes mellitus

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Résumé en anglais	Epidermal growth factor receptor tyrosine kinase (EGFRtk) and endoplasmic reticulum (ER) stress are important factors in cardiovascular complications. Understanding whether enhanced EGFRtk activity and ER stress induction are involved in cardiac damage, and microvascular dysfunction in type 1 diabetes mellitus is an important question that has remained unanswered. Cardiac fibrosis and microvascular function were determined in C57BL/6J mice injected with streptozotocin only or in combination with EGFRtk inhibitor (AG1478), ER stress inhibitor (Tudca), or insulin for 2 weeks. In diabetic mice, we observed an increase in EGFRtk phosphorylation and ER stress marker expression (CHOP, ATF4, ATF6, and phosphorylated-eIF2alpha) in heart and mesenteric resistance arteries, which were reduced with AG1478, Tudca, and insulin. Cardiac fibrosis, enhanced collagen type I, and plasminogen activator inhibitor 1 were decreased with AG1478, Tudca, and insulin treatments. The impaired endothelium-dependent relaxation and -independent relaxation responses were also restored after treatments. The inhibition of NO synthesis reduced endothelium-dependent relaxation in control and treated streptozotocin mice, whereas the inhibition of NADPH oxidase improved endothelium-dependent relaxation only in streptozotocin mice. Moreover, in mesenteric resistance arteries, the mRNA levels of Nox2 and Nox4 and the NADPH oxidase activity were augmented in streptozotocin mice and reduced with treatments. This study unveiled novel roles for enhanced EGFRtk phosphorylation and its downstream ER stress in cardiac fibrosis and microvascular endothelial dysfunction in type 1 diabetes mellitus.
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